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EXAMINER

SISSON, BRADLEY L

ART UNIT

PAPER NUMBER

1655

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/431,451

Applicant(s)

SENAPATHY, PERIANNAN

Examiner

Bradley L. Sisson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-29 is/are rejected.
- 7) ☒ Claim(s) 7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Drawings

1. The drawings are objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Objections

2. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 states that the template is DNA (see step(c), penultimate line). In contrast, claim 7 effectively broadens claim 1 by reciting that the template is now RNA.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance

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presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The amount of experimentation required so to practice the full scope of the claimed invention is profound especially when one considers that the sample can exist in a crude, unpurified state, and that the material can be from virtually any source. The claimed method also encompasses performing hybridization reactions. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

While all of the above issues may not exist in every conceivable format encompassed by the claims, the skilled artisan is no less required to resolve many, if not all of these issues in practicing the full scope of the invention.

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The Amount of Direction or Guidance Provided and The Presence or Absence of Working

Examples

The specification has been found to provide the following prophetic examples:

- “General Approach,” pages 20-24;
- “Specific Amplification of Exons,” page 25;
- “Amplification of the Exons and Their Flanking Regions,” pages 25-28;
- “Isolating other Gene-Control Signal Sequences as Promoters,” pages 29-30; and
- “Arbitrary Sequence Primers as Unique Addresses in a Genome,” pages 31-32.

The specification makes reference to prior art articles as teaching known methods, yet the specification does not provide adequate guidance as to how these prior art methods and conditions are to be modified or adapted so to permit ready application to the full scope of the claimed methods.

The Nature of the Invention

The invention relates to nucleic acid chemistries. More specifically, it relates to performing enzymatic reactions resulting in the generation of amplified copies of a target nucleic acid. The nucleic acid can be from any source, e.g., animal, plant, bacterial, viral, or soil, or a combination of some or all. Further, the claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

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The State of the Prior Art

While performing polymerase chain reaction has been known in the art for some time, the aspect of amplifying a specific target sequence is predicated upon having a primer anneal to a nucleotide sequence that flanks the target region. The primer needs to have a sequence that is sufficiently complementary to the target region that annealing of the primer to the target region is assured. The introduction of random nucleotides “anywhere within” a fixed or constant region introduces an element of unpredictableness.

The Relative Skill of Those in the Art

The skill in the art is high, on par with those holding a Ph.D. in biochemistry and having several years of laboratory experience.

As set forth above, the scope of the claimed methods is immense yet the specification provides but few examples and those are prophetic. While applicant is not as a rule required to provide examples, the unpredictable aspect of the invention, and the paucity of reaction conditions provided, speak to the need for greater guidance so to ensure that one of skill in the art most closely related to the claimed invention can practice the full scope of the claimed invention without having to resort to undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“ ‘[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’ *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) (‘[T]he scope of the claims must bear a reasonable

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correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.'). Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

For the above reasons and in the absence of convincing evidence to the contrary, the specification has not been found to enable the claimed invention.

The predictability or unpredictability of the art

The invention is drawn to chemical reactions, which are recognized by the Court as being unpredictable and deserving of greater levels of disclosure.

The Breadth of the claims

The claims have sufficient breadth of scope so to encompass the amplification of any desired region of any target nucleic acid, regardless of the heterogeneity of the sample and

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without regard to the presence of similar sequences being present. It is further noted that claim 1 requires that one use a “first primer” and a “second primer” in amplifying a target sequence, yet there is no requirement that the primers anneal upstream of the target sequence. Indeed, the first primer may not bind at all to the target sequence. In support of this position, it is noted that the nucleotide sequence of the first primer can be “identical” to the sequence of interest. In such a situation, the first primer could not bind to the sequence. While there is a “second primer” present, the claim does not define how or where the second primer anneals to the target sequence. It is further noted that the first and second primers may comprise “fixed nucleotide sequence” as well as regions of “randomized nucleotide sequence” and that the areas of “randomized sequence” may occur “5’ to, 3’ to, anywhere within, or flanking the region of fixed nucleotide sequence” (emphasis added). With the “fixed” region clearly comprising “random” sequences anywhere within, the “fixed” region is seemingly no more “fixed” than that of the “randomized region.” As shown in the work of Sommer and Tautz, effective annealing can occur with as little as two nucleotides being complementary to the target sequence.

For purposes of examination the claims have been interpreted as encompassing the simultaneous amplification of virtually the entire sequence of any template. In support of this position is the language that “a subset of the plurality of first primers binds to the consensus sequence of interest substantially wherever it occurs in the template and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that DNA regions flanked by the first primer and the second primer are specifically amplified.” With the first and second primers containing randomized sequences of an unspecified length, and that these randomized sequences can occur any place in the length of the primers, including the

critical 3' terminus, and with the claims not requiring the primers contain any identifying feature whereby one would be able to discriminate between the amplification of desired sequences and non-desired sequences, the method would seemingly result in the generation of a hodgepodge of sequences of dubious characteristics.

Response to Argument

At pages 6-9 of the response received 13 August 2001 it is asserted that the case of *Genentech* is non-analogous to the present application; that the subject application is fully enabling; and that any issues withstanding can be resolved by one of skill in the art without undue experimentation. Applicant also directs attention to US patents (page 9), to portions of the subject specification (pages 10-11) as well as to the 132 declaration of Periannan Senapathy.

The above arguments have been fully considered and have not been found persuasive towards the withdrawal of the rejection. As set forth above, the claimed method is considered to have sufficient breadth of scope so to encompassing the simultaneous amplification of virtually the entire sequence of any template. In support of this position is the language that "a subset of the plurality of first primers binds to the consensus sequence of interest substantially wherever it occurs in the template and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that DNA regions flanked by the first primer and the second primer are specifically amplified." With the first and second primers containing randomized sequences of an unspecified length, and that these randomized sequences can occur any place in the length of the primers, including the critical 3' terminus, and with the claims not requiring the primers contain any identifying feature whereby one would be able to discriminate between the amplification of desired sequences and non-desired sequences, the method would

seemingly result in the generation of a hodgepodge of sequences of dubious characteristics. While agreement is reached in part that the characteristics of nucleic acid assays have been resolved to some extent, it is noted that such advances have more plainly identified where problems occur. Just how those problems are to be resolved is not necessarily within the level of skill of the ordinary artisan. In the present case the method of generating a library of amplified sequences does not necessarily result in the production of any desired or useful target sequence and even if it were to, the method does not set forth a repeatable procedure whereby such could be isolated and used. While applicant has directed attention to portions of the specification as evidencing that the specification is enabling, e.g., pages 9-10 of the response where attention is directed to page 4, lines 5-19, and to page 9, lines 7-29 of the disclosure, it is noted that the embodiments set forth in the passage are not limitations found in the claims. It is further note that the specification, not the claims, recites the need for the concentration of primers to be increased "many thousand fold" in order for the assay to proceed "normally." Such required manipulation is not a limitation of the claims and accordingly, has not been read into same.

The 132 declaration of Dr. Periannan Senapathy, Exhibit C, has been fully considered and has not been found to be persuasive towards the withdrawal of the rejection of claims under 35 USC 112, first paragraph. It is noted that the declaration is that of the inventor and not that of a disinterested third party. Further review of the Declaration finds that in each instance the nucleotides found in the 3' region (50% or more of the primer) were fixed and that they did not contain any randomized nucleotides within said region. The claims currently before the Office are not so limited and as such the declaration is not dispositive of the enablement issue.

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5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 12 and 19, and claims that depend therefrom, are indefinite with respect to just what constitutes a “region of fixed nucleotide sequence” and a “region of randomized nucleotide sequence” when the “fixed” region can have interspersed therein random nucleotide sequences.

Said claims are indefinite with respect to just how one can perform any amplification when the first primer, and conceivably the second primer, have the “identical sequence” of the template and the template is single stranded, e.g., RNA (claim 7).

Said claims are indefinite with respect to just what is the second primer directed. In contrast, it is clear that the “first PCR primer” is to result in the amplification of a “consensus sequence of interest... in the template;” however, it is not clear to what the “second PCR primer” is directed. As presently worded it would seem that the first and second PCR primers could well have the same nucleotide sequence, e.g., the randomization of the sequences. While one is expecting that a “subset of the plurality of first primers” is to result in the amplification of the consensus sequence, the method recites no method steps or conditions which would assure that the primers are of a sequence that would properly anneal and that one could somehow check to ensure that the correct sequence was in fact amplified. In support of this position, it is noted that the target sequence could well be found in genomic DNA or in that of a chromosome where the target sequence is flanked by extremely large number of nucleotides. Consequently, the ability

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of the assay to provide an amplification product representative of the full length of the template may not be realized due to the profound length of the template and the operational limitations of PCR. In contrast to the claimed method, the method disclosed in the 132 Declaration clearly shows that 1000X concentration of primers was needed before a reproducible signal was achieved and then the signal was achieved when the annealing conditions were strictly controlled for primers that had "fixed nucleotide sequences" at the 3' terminus.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in cursive script, appearing to read "B. L. Sisson".

Bradley L. Sisson
Primary Examiner
Art Unit 1655

bls

January 14, 2002